SYNTHESIS OF VINYL DERIVATIVES OF TETRAZOLE

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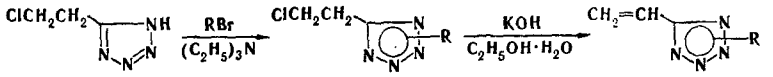
A number of methods for the synthesis of C- and N-vinyl-substituted tetrazoles and closely related tetrazolylalkenes are examined. A preparative method for the synthesis of 5-vinyltetrazoles from the corresponding 5-(β-chloroethyl)tetrazoles by dehydrochlorination of the latter with an aqueous alcohol solution of potassium hydroxide is proposed.

Several variants of the synthesis of C- and N-vinyl-substituted tetrazoles are known. The introduction of a vinyl group in the 5 position of the tetrazole ring can be realized by dehydrochlorination of 5-(chloroethyl)tetrazole [1], by deamination of 1(2)-methyl-5-(diethylamino)tetrazole [2], and also by the direct reaction of acrylonitrile with sodium azide in the presence of aluminum chloride. The first two methods have not been adequately developed methodically, while the latter method makes it possible to obtain 5-vinyltetrazole in only very low yield. Vinyl compounds of the tetrazole series are extremely interesting monomers that are capable of forming polymeric materials with properties of practical value. In this connection, in the present research we examined some possible methods for the synthesis of C- and N-vinyl-substituted tetrazoles and similarly constructed tetrazolylalkenes.

One of the most widely used methods for the formation of a vinyl group is the dehydrochlorination of chloroethyl-substituted compounds. Although this method for the construction of 5-vinyltetrazole is, at first glance, more laborious than the synthesis from acrylonitrile and sodium azide, the accessibility of 5-(β-chloroethyl)tetrazole (I) [1] and its 1- and 2-alkyl derivatives (II) [3] opens up a route to the preparative synthesis of 5-vinyltetrazoles. When the dehydrochlorination is carried out in aqueous solutions of alkali metal hydroxides in increased volumes, it is accompanied by spontaneous polymerization of the resulting vinyltetrazole. To eliminate this effect, the dehydrochlorination step should be carried out in an aqueous solution of potassium hydroxide. This makes it possible to obtain reproducible and completely satisfactory yields of 5-vinyltetrazole (IIIa) and its ethyl derivative (IIIb).



I II IIIa,b

II, III b R = C_2H_5; III a R = H

Unfortunately, this method cannot be realized in the case of the synthesis of aryl-substituted 5-vinyltetrazoles because of the fact that 5-chloroethyl-1(2)-aryltetrazoles are difficult to obtain. In order to introduce a double bond in the 5 position of a tetrazole ring containing a phenyl substituent we used the Wittig reaction. The formation of phosphonium salt IV from 1-phenyl-5-chloromethyltetrazole V and dehydrochlorination proceeds without any anomalies and gives phosphinylalkylidene VI in 60% yield. The latter reacts quite smoothly with various aldehydes via the generally accepted scheme. This reaction makes it possible to obtain olefins of the tetrazole series (VII) with various degrees of unsaturation in good yields.

The corresponding methyl tetrazolylacrylates (Xa, b), which, like VII, have trans structures, are readily obtained by the reaction of 1-phenyl-5-formyltetrazole (VIII)

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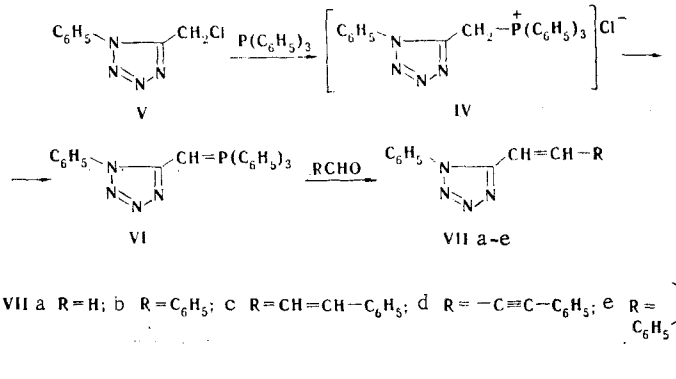
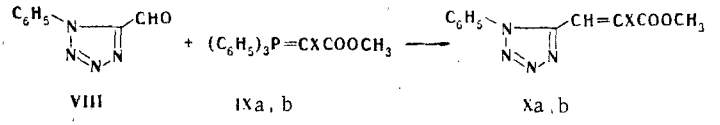
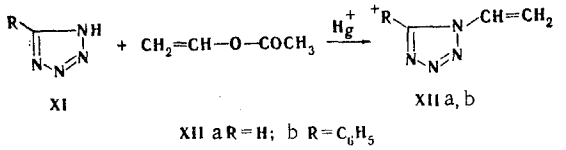


with carbomethoxybromomethylenephosphorane (IXb). The spin–spin coupling constants (SSCC) of the protons of the double bond of olefins VIIb-e and IXa range from 16.3 to 17.1 Hz.



A scheme involving the dehydrohalogenation of N-chloroethyltetrazoles has been proposed for the synthesis of N-vinyl derivatives of tetrazole [4]. The application of this method in our case involves alkylation of the sodium salt of the tetrazole with ethylene chlorohydrin and the necessity for separation of the two isomers formed. It has been established that whereas the isomers of 5-substituted chloroethyltetrazoles can be isolated in individual form, it is not possible to separate the mixture of isomers of 1- and 2-(β-chloroethyl)tetrazoles [4]. In addition, the replacement of the hydroxy group by chlorine and the subsequent dehydrochlorination proceed with considerable resinification and give the 1(2)-vinyltetrazoles in low yields.

The production of N-vinyltetrazoles on the basis of the reaction of vinyl isocyanide [5] and vinyloxazolones [6] with nitrous acid is not a preparative method. In this connection, we examined a scheme for the vinylation of tetrazoles (XI) with vinyl acetate in the presence of mercurous acetate in acetic acid at 45-55°C:



As a result of this reaction in the case of tetrazole and 5-phenyltetrazole we obtained the corresponding 1-vinyl-substituted tetrazoles (XII) in 60-68% yields, in addition to very small amounts of a second isomer, which was easily separated by distillation. The PMR spectrum contains signals of protons of a vinyl group (7.48 and 5.40, 6.07 ppm).

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Varian H-100 spectrometer with hexamethyldisiloxane as the internal standard. 1-Phenyl-5-chloromethyltetrazole (V) [8], 5-(β-chloroethyl)tetrazole (I) [1], and 2-ethyl-5-(β-chloroethyl)tetrazole (II) [3] were obtained by known procedures.

5-Vinyltetrazole (IIIa). A solution of 84 g of potassium hydroxide in 200 ml of water was added with stirring to a suspension of 100 g (0.75 mole) of 5-(β-chloroethyl)-tetrazole in 380 ml of ethanol in the presence of the stabilizer Ionol, and the reaction mixture was stirred at 78-80°C for 4 h. It was then cooled, and the potassium chloride was removed by filtration. The filtrate was evaporated *in vacuo* to one third of its original volume, 600 ml of chloroform was added to the residue, and the resulting mixture was acidified to pH 2 with 15% hydrochloric acid. The aqueous layer was extracted three times with chloroform (100-ml portions), and the combined extracts were dried over magnesium sulfate. The solvent was removed by vacuum distillation, and the residue was recrystallized

TABLE 1. Vinyltetrazoles and Their Derivatives

Compound	mp or bp, °C (mm)	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
IIIa	126—127	1650	37,3	4,6	57,8	$C_3H_4N_4$	37,7	4,4	58,0	79
IIIb	52—54 (1)	1650, 3040, 3110	48,6	6,6	45,1	$C_8H_8N_4$	48,4	6,5	44,9	78
VIIa	85,5—90	1600, 1635	63,0	4,9	32,0	$C_9H_8N_4$	62,7	4,6	32,5	52
VIIb	183—184*	1600, 1635	73,0	5,3	22,1	$C_{15}H_{12}N_4$	72,6	4,8	22,6	73
VIIc	161—162	975, 990, 1600, 1635	74,4	5,1	20,5	$C_{17}H_{14}N_4$	74,5	5,1	20,4	74
VIId	145—146	951, 1600, 1627, 3202	75,7	4,6	20,6	$C_{17}H_{12}N_4$	75,4	4,4	20,5	47
VIIe	188—190	1600, 1630	70,4	4,4	25,1	$C_{23}H_{17}N_7$	70,6	4,3	25,1	75
Xa	70—71	1170, 1240, 1660, 1720	57,8	4.4	24,6	$C_{11}H_{10}N_4O_2$	57,3	4,3	24,3	65
Xb	112—113	1650, 1720	43,0	2,9	18,1	$C_{11}H_9N_4O_2Br$	42,7	2,9	18,1	80
XIIa	97—98 (1)	910, 1640	37,5	4,5	58,3	$C_3H_4N_4$	37,7	4,4	58,0	60
XIIb	38—39	910, 1645	62,6	4,6	32,5	$C_9H_8N_4$	62,7	4,6	32,5	68

*According to the data in [7], this compound has mp 182-183°C.

from chloroform to give 56.9 g (79%) of a product with mp 126-127°C. The principal characteristics of the compounds obtained are presented in Table 1.

(1-Phenyl-5-tetrazolyl)methyltriphenylphosphonium Chloride (IV). A solution of 5.8 g (0.03 mole) of 1-phenyl-5-chloromethyltetrazole (V) and 8.4 g (0.03 mole) of triphenylphosphine in 30 ml of dioxane was refluxed for 3 h, after which it was cooled, and the precipitated chloride was removed by filtration and washed with ether to give 10 g (78%) of a product with mp 260-261°C. Found: C 68.6; H 4.9; Cl 7.2; N 12.4%. $C_{26}H_{23}ClN_4P$. Calculated: C 68.2; H 5.0; Cl 7.6; N 12.2%.

(1-Phenyl-5-tetrazolyl)methylenetriphenylphosphorane (VI). A 40% solution of sodium hydroxide was added to a suspension of 9.1 g (0.02 mole) of phosphonium chloride IV in 50 ml of water until a persistent pink coloration developed (with respect to phenolphthalein). The resulting precipitate was removed by filtration and recrystallized from benzene to give 5 g (60%) of a product with mp 210-211°C. Found: C 74.4; H 5.2; N 13.8%. $C_{26}H_{21}N_4P$. Calculated: C 74.3; H 5.0; N 13.4%.

Reaction of (1-Phenyl-5-tetrazolyl)methylenetriphenylphosphorane with Aldehydes. A solution of 0.8 g (0.002 mole) of ylid VI and 0.002 mole of the aldehyde in 10 ml of benzene was refluxed for 3 h, after which it was cooled, and the precipitated triphenylphosphine oxide was separated by filtration. The benzene solution was evaporated to dryness, 5 ml of ethanol was added to the residue, and the olefin was removed by filtration and recrystallized from alcohol. The principal characteristics of the VIIa-e are presented in Table 1.

Methyl-3-(1-Phenyl-5-tetrazolyl)acrylate (Xa). A solution of 0.35 g (0.002 mole) of 1-phenyl-5-formyltetrazole in 5 ml of benzene was added to a solution of 0.7 g (0.002 mole) of carbomethoxymethylenetriphenylphosphorane (IXa) in 5 ml of benzene, and the mixture was maintained at 20-25°C for 1.5-2 h. The benzene was removed, and the reaction mixture was extracted with ether. The solution was dried, and the ether was removed *in vacuo*. The residue was passed through a column filled with aluminum oxide by elution with ether—petroleum ether (1:1), after which the solvent was evaporated, and the residual crystals were recrystallized from a mixture of benzene with petroleum ether (1:1). The yield was 0.3 g (65%).

Similarly, 0.5 g of methyl 2-bromo-3-(1-phenyl-5-tetrazolyl)acrylate (Xb) was obtained from 0.8 g (0.002 mole) of carbomethoxybromomethylenetriphenylphosphorane and 0.35 g (0.002 mole) of formyltetrazole VIII.

1-Vinyltetrazole (XIIa). An 8.4-g sample of tetrazole and 0.1 g of Ionol were added to a solution of 4 g of mercurous acetate and 1.2 g of concentrated H_2SO_4 in 50 ml of vinyl acetate, after which the mixture was stirred at 50°C for 15-20 h. The excess vinyl acetate was then removed by vacuum distillation, and 100 ml of dry methylene chloride and 8 g of anhydrous potassium acetate were added to the residue. The precipitated mercurous acetate was removed by filtration, and the filtrate was dried with magnesium sulfate and distilled

in vacuo to give 6.9 g (60%) of product. PMR spectrum: 5.40 and 6.07 (=CH_2, J = 1.7 Hz); 7.48 (—CH=); 9.34 ppm (C_5—H).

1-Vinyl-5-phenyltetrazole (XIIb) was similarly obtained in 68% yield. PMR spectrum: 5.43 and 6.24 (=CH_2, J = 1.2 Hz); 7.64 (—CH=); 7.48-8.15 ppm (5H, aromatic protons).

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